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The Emergence of Quantitative Systems Toxicology

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Achieving a Pathway-based Approach to More Efficient Chemical Risk Assessment

Quantitative systems toxicology (QST), a subset of systems biology, is the integration of classical toxicology with quantitative analysis of large networks of molecular and functional changes occurring across multiple levels of biological organization. A goal of QST is to characterize adverse drug reactions (ADRs) by describing modes of action as adverse outcomes pathways and perturbed networks versus conventional empirical end points and animal-based testing. Since QST is at the juncture of Systems Biology with toxicology and chemistry it is important to understand systems biology and the transformational role it plays in how biological systems are investigated.

What is Systems Biology and how has it led to a better understanding of disease diagnosis, progression, treatment, and prevention?

Contrary to the classical reductionist tactics where the linear behavior of biological systems can be explained by properties of components, systems biology maintains that biological systems have emergent properties that can only be determined in a system as a whole and not its constituent parts. Systems biology, which emerged at the start of the 21st century, applies a nonlinear, integrative, quantitative, and holistic approach using an interdisciplinary mix of biology, computational modeling, engineering, bioinformatics, and other sciences to understand the complexity of biological systems. The underlying basis of this "whole is greater than the sum of the parts" paradigm is to decipher how complex interactions give rise to the function and behavior of specific biological systems, eg, cell signaling networks or enzymes/metabolites in a metabolic pathway. The fundamental basis of systems biology is a "network of networks"—how all components of each network inter- and intra-connect, their functions, and how they change in response to a perturbation. The emergence and evolution of "omics" technologies—genomics, proteomics, transcriptomics, metabolomics, and others, are the underlying building blocks of systems biology research.

The systems biology approach has led to better understanding of how diseases result from perturbations of biological networks. Applying systems biology approaches to medical research—systems biomedicine—will lead the way to more powerful models for prevention, diagnosis, treatment, and prognosis of disease.

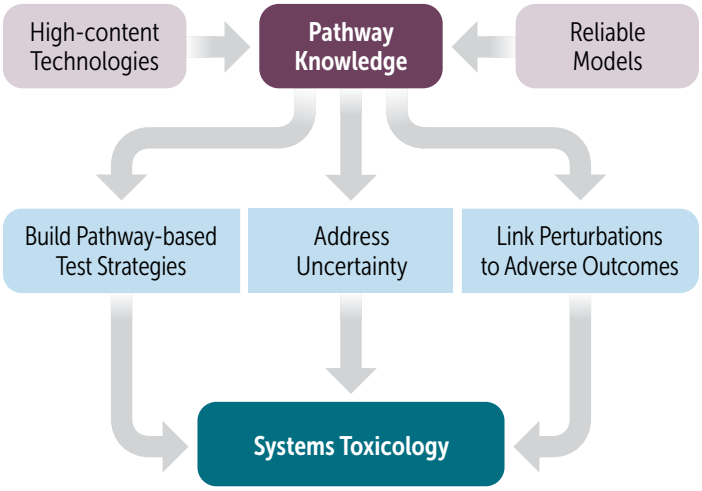
The challenges of predicting toxicity early in the drug discovery process

A major challenge for sponsors in developing efficacious and safe drugs is the ability to understand and effectively predict adverse effects of xenobiotic substances on extremely complex biological systems early in the drug discovery process. An alarming fact is that thirty percent of adverse drug reactions (ADRs) cannot be predicted by current pre-clinical animal testing and existing modeling methodologies. ADRs remain a major complication of patient therapy and impede the development of new, safe, and efficacious drugs. The availability of vast amounts of high quality omics data (eg, genomics, proteomics, transcriptomics, metabolomics) and relational databases, combined with advanced computational and analytical tools such as high-throughput screening (HTS) methodologies, has spurred a move towards QST modeling to better understand the mechanistic basis of ADRs, and achieve a more predictive and accurate approach to risk assessment.

Systems Toxicology—a quantitative approach to better predict adverse drug reactions

Systems toxicology is a mechanistic approach to risk assessment that integrates *in vitro* and *in vivo* toxicity data with computational modeling to better understand how perturbations by xenobiotic agents effect biological systems. Current toxicology methods focus on individual pathways or proteins, which do not provide sufficient understanding into the mechanism of action of chemicals that perturb biological processes in human cells and tissues. Contrary to traditional toxicology, systems toxicology takes a large scale computational network approach to risk assessment. Systems toxicology integrates data generated from animal or *in vitro* studies and immense information from functional genomics, proteomics, transcriptomics, and other omics technologies. This, combined with advanced methods of high throughput screening, results in the ability to examine emergent properties of biological systems, which otherwise would not be uncovered using classical toxicology methods. Biological network perturbations are key to comprehending the underlying link between xenobiotic agents and their effects on health.

Systems Toxicology: The Integration of *In Vitro* and *In Vivo* Data with Computational Modeling



The use of computational models to understand mechanisms of toxicity

Multiple approaches for systems toxicology take into account how well the mechanisms and the biology is understood and characterized which, in turn, will determine the approach best suited for the questions that need to be answered. At a very high level, computational approaches that exist for systems toxicology are a great complement and can add significant benefit across early drug discovery through late phases of the drug development pipeline. Systems toxicology approaches can include the use of relational databases and mechanistic models. Relational databases can be used to ascertain exposure-response relationships. Small- or large-scale computational models can be built to better understand the mechanism of toxicity, resulting in improved prediction of ADRs.

Regulatory adoption and current exploration into the development of systems toxicology for risk assessment

Regulatory, biomedical, and public health research agencies including the US Food and Drug Administration (FDA), US Environmental Protection Agency (EPA), European Medicines Agency, National Institutes of Health (NIH), National Institute of Environmental Health Sciences (NIEHS), and the European Commission of Public Health and Safety, have made concerted efforts into the exploration of systems toxicology to achieve more efficient safety assessments. Consortia, including Trans QST and the collaboration between EU-ToxRisk and Toxicology in the 21st Century (Tox 21), have established initiatives to enhance scientific capabilities and improve safety assessment approaches based on alternatives to animal testing.

Certara's Simcyp Quantitative Systems Toxicology Initiative

Our Simcyp Division, leaders in physiologically-based pharmacokinetic (PBPK) modeling and simulation, has established a new QST initiative that will focus on understanding the mechanistic determinants of drug toxicity and the development of predictive QST software tools. Leveraging Simcyp's quantitative system pharmacology (QSP) expertise, the combined integrated efforts will provide a holistic, quantitative approach to simultaneously assess drug efficacy, safety, and therapeutic index.To augment our strategic commitment to QST, Simcyp has been awarded three significant grants to accelerate the move towards systems toxicology using mechanism-based chemical safety testing strategies. These grants were awarded by the following systems toxicology initiatives:

- **EU ToxRisk/Tox 21**—a collaboration between EU ToxRisk and Tox 21 established to reduce the use of animals and achieve more efficient chemical safety assessments
- **Trans QST**—a consortium comprised of expert centers across the EU whose aim is to assemble and curate, in a form amenable to quantitative systems modelling, large existing datasets and European Federation of Pharmaceutical Industries and Associations (EFPIA) legacy data, as a framework for collaborative projects
- **eTranSafe**—an organization that focuses on Translational Safety and the integration of pre-clinical and clinical data to analyze the predictive robustness of animal studies

Benefits of QST

Traditional approaches to safety assessment, using *in vitro* and *in vivo* assays, greatly depend on animal testing and provide limited mechanistic information. In addition, the increased concerns over risks associated with chemical exposure create a substantive need for more predictive and accurate approaches to risk assessment. QST, as a subset of Systems Biology, takes a computational approach to integrate large amounts of *de novo* and legacy data to gain new insights into the link between molecular interactions and adverse effects. The potential of QST offers significant promise to drug discovery and development:

- Decrease the cost and time to bring new drugs to market by identifying drug toxicity earlier in the drug discovery/drug development pipeline
- Derive increasingly predictive models that better forecast the impact of xenobiotic substances on biological systems

- Increase drug efficacy, reduce ADR risk, and decrease off-target interactions
- Strengthen drug safety assessments and reduce animal testing through the implementation of mechanism-based chemical safety testing strategies
- Gain better understanding of disease progression and drug-induced toxicity to foster the development of safe, targeted and efficacious network-based drugs
- Identify new biomarkers for predictive, preventive and personalized healthcare

The integration of classical toxicology with more reliable and advanced in vitro testing methods, advanced screening technologies, omics data, and in silico modeling strategies, such as PBPK, are key elements of a systems approach to more effective chemical risk assessment. QST offers great potential to better understand disease progression and, ultimately, develop safe, more efficacious drugs.

Systems toxicology integrates classical toxicology approaches with omics technologies, advanced high-throughput screening methods, and mechanistic computational models to predict toxicity.

System toxicology holds significant promise for drug discovery and development by providing

- improved prediction of ADRs
- reduced animal testing
- increased drug efficacy
- greater understanding of disease progression

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About Certara

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